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Ichthyosis-Characteristic Appearance-Mental Retardation Syndrome With Distinct Histological Skin Abnormalities

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In this report, we describe a 2.5-year-old severely mentally retarded boy with peculiar appearance and generalized ichthyosis, born to consanguineous Turkish parents. The histological finding in the skin biopsy of unusually large oval keratohyalin granules in the granular cells is unique, and hitherto has not been reported in other ichthyosis-mental retardation syndromes.

KEY WORDS: ichthyosis, megalocornea, multiple congenital anomalies, cleft palate

INTRODUCTION

Ichthyosis is a heterogenous phenotype, which can be classified according to histological findings on skin biopsy, associated clinical findings and inheritance pattern. We present a child from consanguineous parents with congenital ichthyosis and unique skin histologic findings, associated with mental retardation and minor craniofacial anomalies.

CLINICAL REPORT

D.M., a male, is the second child of young and healthy parents. The first child, a 5-year-old boy, is normal. The parents are first cousins, and of Turkish origin. Otherwise family history is unremarkable. Pregnancy was normal, except that the mother experienced fetal movements always at the same place. Labor started at 42 weeks and failed to progress over 3 days, with very poor contractions. At birth, the child was cyanotic but no major problems were otherwise noted during the first days of life. Birth weight was 4.2 kg (75th–97th centile) and length was 52 cm (75th centile). At birth he had a cleft palate, surgically repaired at the age of 1.5 years, and a left inguinal hernia, repaired at the age of one month.

Psychomotor retardation was severe from the beginning, with major feeding problems. Two episodes of febrile convulsions occurred at the ages of 1 and 2 years. Now, at the age of 2.5 years, social contact is very poor. He does not speak, and expresses only a few sounds. Motor development is equally severely retarded: he started to sit without support at the age of 18 months, but cannot stand or walk. There is no pince grasp and he has generalized hypotonia. Biometry is normal: length 88 cm (10th centile), weight 13.5 kg (50th centile) and OFC 49 cm (25th centile).

A distinct craniofacial appearance is evident, with brachycephaly (Fig. 1a,b), a remarkably round face, hypertelorism, long eyelashes and large corneae (diameter of 13 mm). The ears are large and protruding. He also had a large mouth, with fine lips and macroglossia. The uvula is bifid. The hands and feet are broad and there is a clinodactyly of the fifth fingers.

There is a generalized ichthyosis (Fig. 2), present from birth onward, and most prominent in the neck, the axillary and inguinal region and around the umbilicus. The scaling is fine, with a slight dark discoloration of the lesions. Hair and nails appear normal.

Up to now, several additional investigations have been performed all with normal results: brainstem auditory-evoked responses, CT scan of the brain, X-ray skeletal survey, chromosomal analysis on peripheral blood lymphocytes and on skin fibroblasts, electroencephalography and scanning electron microscopic examination of scalp hairs. Ophthalmological examination confirmed the presence of megalocornea without associated anomalies.

Microscopic examination of a skin biopsy taken from the left forearm was consistent with the diagnosis of ichthyosis, with the presence of a partially compact orthokeratotic hyperkeratosis of the stratum corneum (Fig. 3). The granular layer is present and the granular cells contain unusually large keratohyalin granules. This is confirmed by electron microscopic examination,

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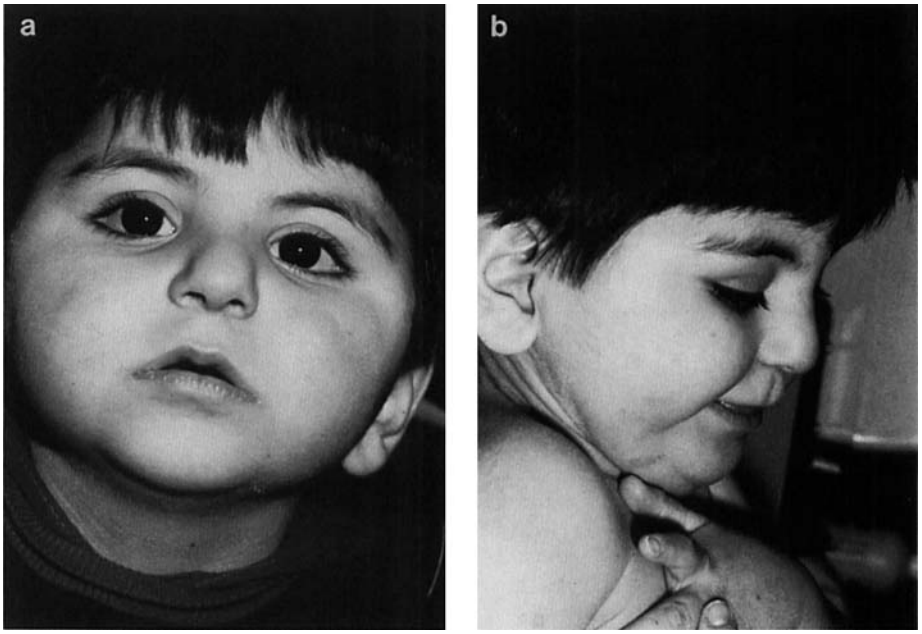


Fig. 1. **a, b:** Facial appearance.

which shows swollen granular cells with one or more very large oval keratohyalin granules (Fig. 4a). The cells of the stratum corneum have a very dense cytoplasma, the most superficial cells being oedematous and electron-lucent (Fig. 4b). The cells do not contain lipid droplets nor cholesterol crystals, and show no membrane accumulations. The dermis and hypodermis are normal and no abnormalities in the other keratinocyte layers, or at the dermo-epidermal junction are found.

DISCUSSION

This boy, born to consanguineous parents of Turkish origin, has a severe developmental delay associated with generalized ichthyosis and remarkable craniofacial symptoms and signs, i.e., brachycephaly, round plethoric face, megalocornea, large mouth and big ears, macroglossia and cleft palate. The association of ichthyosis and mental retardation is well-known and has been documented in an increasing number of genetic

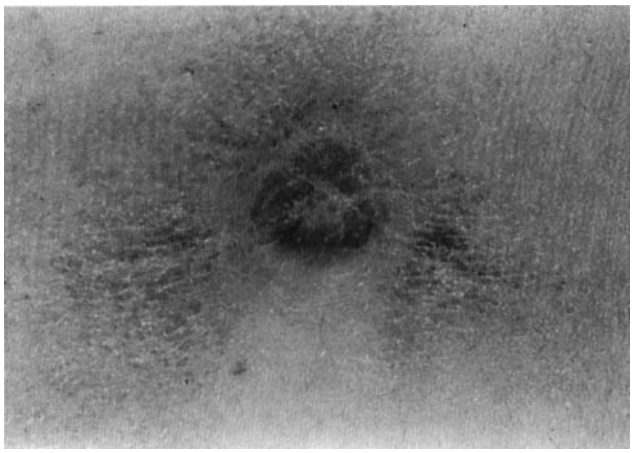


Fig. 2. The fine ichthyotic scaling around the umbilicus is shown, with a slight dark discoloration.

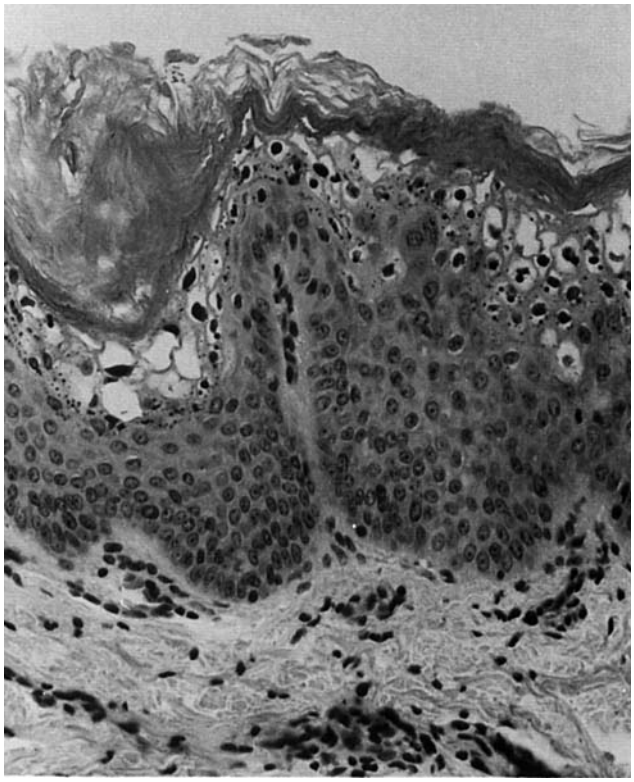
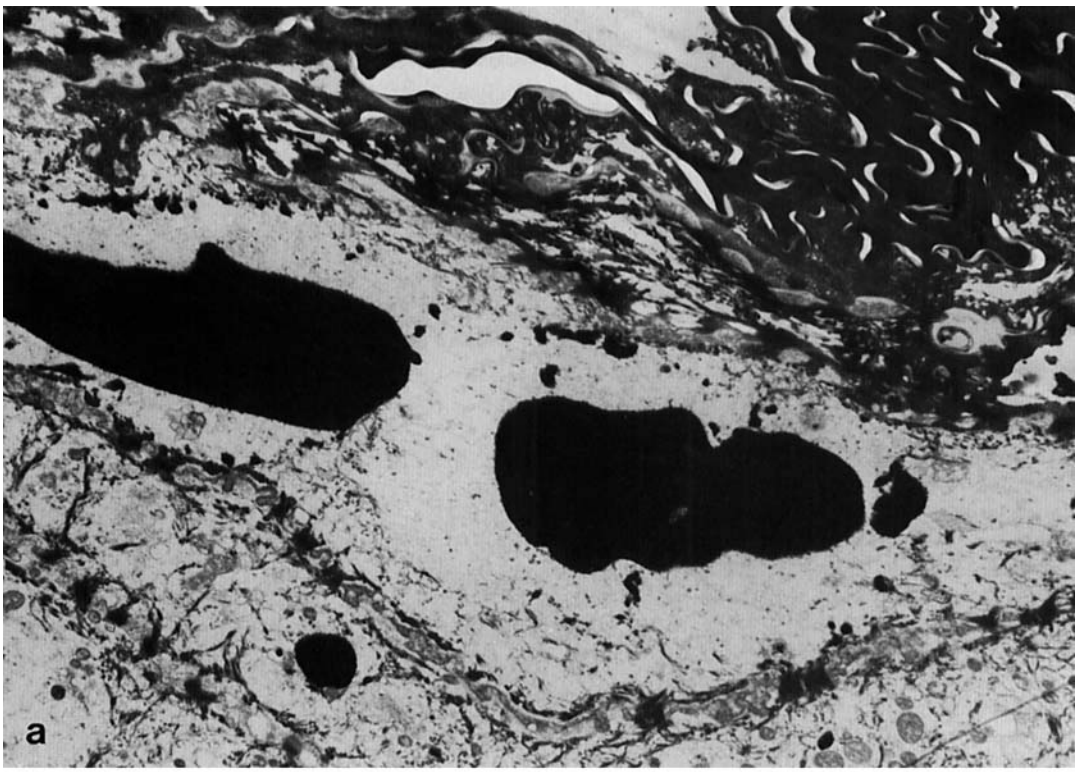


Fig. 3. Light microscopy of skin biopsy, showing hyperkeratosis and a granular layer containing unusually large keratohylin granules. Many granular cells are swollen and vacuolated. Haematoxylin and eosin. Magnification ×130.



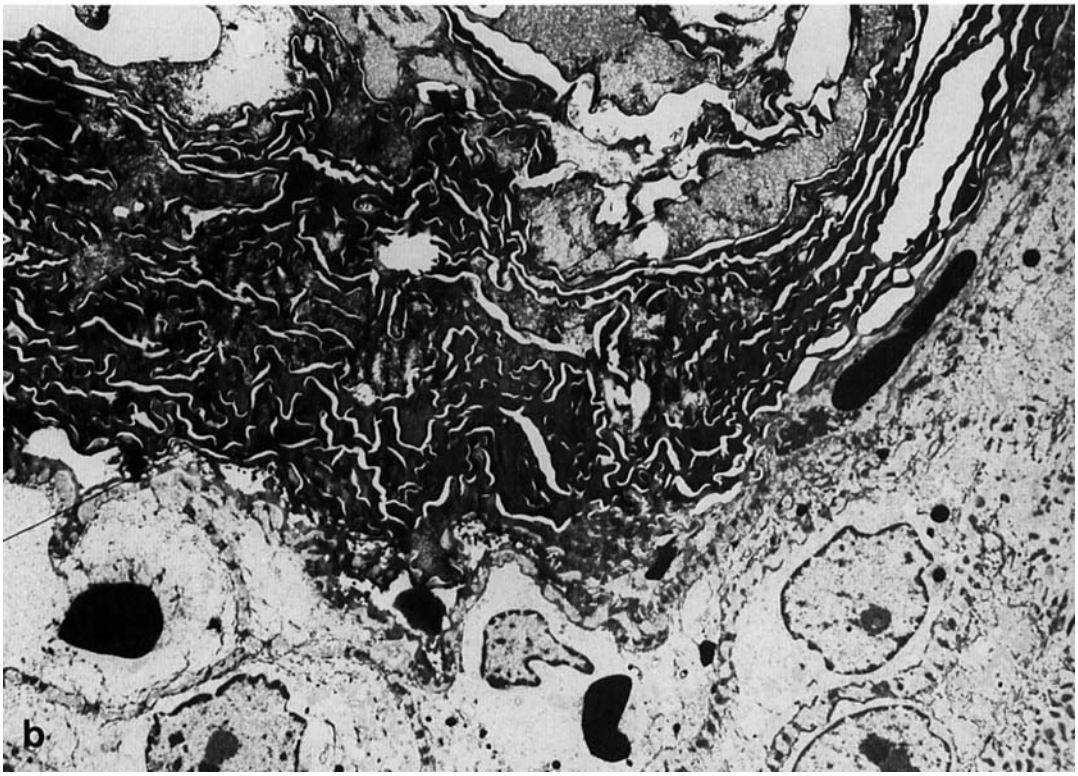


Fig. 4. Electron micrographs of part of the epidermis. **a:** Swollen granular cells with very large oval keratohyalin granules. Magnification × 9,200. **b:** Cells of the stratum corneum with dens cytoplasm. The superficial cells are oedematous and electron lucent cells. Below, granular cells with large oval keratohyalin granules. Magnification × 3,680.

syndromes in the past, e.g., Sjögren-Larsson syndrome [Jagell et al., 1981], infantile Refsum disease [Scotto et al., 1982] and rhizomelic chondrodysplasia punctata [Spranger et al., 1971].

Histological and electron microscopical examination of the skin biopsy of the present patient demonstrated large, oval keratohyalin granules in the granular cells. This unique observation has, as far as we know, never been reported in any of the well-defined types of ichthyosis such as X-linked ichthyosis with steroid sulfatase deficiency [Feinstein et al., 1970]. In ichthyosis-neutral lipid storage disease, hypotonia and developmental delay have been described [Chanarin et al., 1975]. Pathognomonic for this condition is the presence of cytoplasmatic lipid droplets, which were lacking in the skin biopsy of the present patient. In Ichthyosis bullosa of Siemens, mutations in the keratin 2e gene have recently been demonstrated [Kremer et al., 1994]. The clinical and pathological findings in the present patient differ from this condition [Traupe et al., 1986].

The association of mental retardation-ichthyosis and cleft palate has been described by Zunich in a few children, including two sibs [Zunich and Kaye, 1983, 1984; Zunich et al., 1988]. The present boy shares some of the manifestations with these cases, such as cleft palate, hypertelorism and brachycephaly. However, these children also had retinal coloboma, conductive hearing loss and a congenital heart defect in some. In addition, the histological findings were clearly different from the distinct abnormalities seen in the present patient [Zunich et al., 1985].

The cause of the disorder in this child is not known. The finding of extremely large keratohyalin granules may provide a means towards the understanding of the pathogenesis of the ichthyosis. The cause of the neurological symptoms and minor anomalies remains elusive. As with most mental retardation-ichthyosis disorders, a genetic cause is likely, and since the parents were consanguineous, autosomal recessive inheritance is probable.

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